DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration

STATEMENT OF

RANDALL LUTTER, PH.D.
DEPUTY COMMISSIONER
FOR POLICY

FOOD AND DRUG ADMINISTRATION
BEFORE THE

SUBCOMMITTEE ON HEALTH

COMMITTEE ON ENERGY AND COMMERCE

UNITED STATES HOUSE OF REPRESENTATIVES

"Legislative Hearing on Discussion Drafts Concerning Prescription Drug User Fee Act Reauthorization, Medical Device User Fee and Modernization Act Reauthorization, Drug Safety, and Certain Pediatric Pharmaceutical and Device Legislation"

June 12, 2007

RELEASE ONLY UPON DELIVERY

Introduction

Mr. Chairman and Members of the Subcommittee, I am Randall W. Lutter, Ph.D., Deputy Commissioner for Policy at the U.S. Food and Drug Administration (FDA or the Agency). I am pleased to be here today to talk about discussion drafts to reauthorize several statutes of vital importance to our mission to protect and promote the public health, as well as enhancements to our current authorities in the areas of pediatric devices and drug safety.

The Administration strongly supports the reauthorization of the prescription drug user fee and medical device user fee programs. These user fee programs expire at the end of September 2007, and their timely reauthorization is critical to the ability of FDA to continue to bring safe and effective drugs, biologics, and devices to market to the benefit of the health of Americans in a timely manner. We also support timely reauthorization of the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA), as these two statutes are essential to gathering much needed information required in the safe and effective use of medicines in children. I would like to emphasize the importance of timely reauthorization of these laws in order to avoid any disrupting key ongoing and effective programs. We hope to work with Congress to ensure timely passage of legislation that maintains the effective work of these statutes.

Prescription Drug User Fee Act (PDUFA)

FDA's review of new drug applications (NDAs) and biologics license applications (BLAs) is central to FDA's mission to protect and promote the public health. In 1992, Congress enacted PDUFA to speed drug application review, and subsequently has reauthorized it twice.

PDUFA has produced significant benefits for public health, including providing the public access to over 1,200 new drugs and biologics. While maintaining our rigorous review standards, we now review drugs as fast as or faster than anywhere in the world. The median approval time for priority new drug and biologic applications has dropped from 14 months in fiscal year (FY) 1993 to only six months in FY 2006. During the PDUFA era, FDA reviewers have approved approximately:

- 76 new medicines for cancer;
- 178 anti-infective medications (including 56 for treatment of HIV or Hepatitis;
- 111 medicines for metabolic and endocrine disorders;
- 115 medicines for neurological and psychiatric disorders; and
- 80 medicines for cardiovascular and renal disease.

We have complied with provisions of the most recent PDUFA reauthorization directing FDA to consult with the House Committee on Energy and Commerce, the Senate Committee on Health, Education, Labor, and Pensions, and stakeholders in developing recommendations for PDUFA reauthorization. We believe that the Administration's proposal places PDUFA on a sound financial footing, enhances pre-market review, and creates a modern post-market drug safety system that follows products throughout their

full life cycle. Importantly, the proposal also supports new user fees to support the review of direct-to-consumer television advertisements voluntarily submitted to FDA for review prior to airing. We are pleased that the discussion draft is generally consistent with the Administration's recommendations. However, one significant concern to us is the proposal to fund new drug safety activities (outside of those included in the PDUFA proposal) with user fees. In our view the amount that could be raised through user fees could be inadequate to support the new activities. In addition, we are concerned that reopening the PDUFA IV proposal in this manner represents a change in the process for developing user fee programs.

Medical Device User Fee and Modernization Act (MDUFMA)

Similarly, FDA's review of medical device applications is essential to FDA's mission. In 2002, Congress enacted MDUFMA to reduce the time necessary for new medical device application review. As with PDUFA, the medical device user fee program is scheduled to expire on September 30, 2007.

The user fees provided by MDUFMA, and annual appropriations, have allowed us to make significant improvements in the device review program. Since MDUFMA was enacted, FDA has approved more than 150 original PMAs. The following devices intended to address unmet needs in the pediatric population were approved: the first pediatric left-ventricular assist device, a cooling cap to treat severe hypoxic-ischemic encephalopathy in infants, and an expandable prosthetic rib to treat growing children with Thoracic Insufficiency Syndrome.

The device review program also has approved important new laboratory tests, including: the first test for use as an aid in diagnosing West Nile Virus; tests for diabetes management and newborn screening; tests for diagnosing cystic fibrosis; and a rapid screening test for lead poisoning that can be used at health care clinics, mobile health units, and schools.

In the area of women's health, FDA's device review program approved: an optical detection system to identify areas of potential cervical cancer; a non-invasive therapy system to treat uterine fibroids with high-frequency ultrasound; and a clinical laboratory test to determine if a woman with breast cancer is a good candidate for Herceptin therapy. FDA approved other important devices including: the first carotid-stenting systems; a hip resurfacing system intended to treat younger patients who are not ready for hip replacements; and the first over-the-counter automatic external defibrillators.

In preparing our proposed recommendations for MDUFMA reauthorization, as with PDUFA, we have consulted with the House Committee on Energy and Commerce, the Senate Committee on Health, Education, Labor, and Pensions, and stakeholders. We believe our proposal would ensure sound financial footing for the device review program and would enhance the process for pre-market review of device applications. It would change the fee structure of user fees to provide more adequate and stable funding for FDA while maintaining predictability in fees for the medical device industry. Importantly, we also recommend modest modifications to the third party inspection program authorized by MDUFMA that will streamline the program in order to increase participation, while maintaining important safeguards against potential conflicts of

interest. FDA finds significant problems with the existing third party accredited person inspection program, which has garnered minimal industry participation to date. A more robust third party program would permit FDA to focus its resources on establishments and products posing the greatest risk to public health. While we are pleased that much of the discussion draft is consistent with the Administration's proposed recommendations, we are disappointed that these important modifications have not been included. We recommend that these modifications be added to the drafts and note that in the absence of modifications, FDA will continue to expend resources to maintain the program without enhancing its inspectional capabilities.

Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA)

The Administration supports reauthorization of the Best Pharmaceutical for Children's Act (BPCA) and the Pediatric Research Equity Act (PREA) (now called the Pediatric Research Improvement Act [PRIA]). Congress enacted both of these initiatives to promote development of drugs for children because information was inadequate to ensure proper use in children of the majority of drug products approved in the U.S. Together these statutes have transformed information about safety and efficacy for children of important therapeutics and promoted safety and innovation in pediatric drug development. However, we are concerned that the discussion drafts, as presently drafted, contain provisions that could have an unintended and negative impact on these successful programs. I will summarize the successes of these statutes and then comment on certain proposed changes in the discussion draft.

The six-month exclusivity incentives for pediatric studies provided by BPCA has had a powerful impact on providing important, safety, efficacy, and dosing information for drugs used in children. BPCA also expanded and enhanced the initial pediatric exclusivity process by authorizing FDA to establish the Pediatric Advisory Committee (PAC), and provided for post-marketing safety review by PAC of all pediatric products granted exclusivity by FDA. BPCA also promotes transparency by requiring that summaries of the studies conducted under the BPCA be posted regardless of the regulatory action (e.g., approval, non-approval). In addition, BPCA created the Office of Pediatric Therapeutics which, as part of FDA's Office of the Commissioner, provides scientific expertise and ethics advice, and coordinates and facilitates activities that may have any affect on the pediatric population or the practice of pediatric medicine, or may involve pediatric issues.

In contrast to BPCA, which provides a voluntary mechanism for obtaining needed studies on either approved or unapproved indications for a given drug, PREA requires pediatric assessments (based on studies in pediatric populations) of certain drugs and biological products. This requirement is only in the indications that are approved or for which the sponsor is seeking approval, and only under certain circumstances. PREA includes provisions allowing FDA to defer or waive the required pediatric assessments under limited circumstances. As with BPCA, PREA has been successful in generating pediatric studies on many drugs and helping to provide important new information in product labeling.

Together, BPCA and PREA have encouraged the development of important new safety, effectiveness, and dosing information for drugs used in children and led to numerous labeling changes. Since 1997, the exclusivity incentive program has generated labeling changes for 128 products. The labeling changes have significantly increased the information available to health care professionals to use in the treatment of pediatric patients:

- the labeling for 83 products has been updated to include new information expanding use of the product to a broader pediatric population;
- the labeling of 25 products had specific dosing adjustments;
- the labeling of 28 products was changed to show that the products were found **not** to be safe and effective for children; and
- 37 products had new or enhanced pediatric safety information added to the labeling (these numbers add up to a number greater than 128 because some products had more than one change to the labeling).

Since PREA was enacted, there have been approximately 300 applications which have fallen within the scope of the PREA requirements. FDA has approved approximately 40 labeling changes involving pediatric studies linked to PREA assessments since the enactment of the legislation in 2003.

However, the draft legislation contains several provisions that we believe will have a severe negative impact on these successful programs. The BPCA incentive to conduct clinical trials for children will be compromised and the creation of an internal review committee for both BPCA and PREA programs and other program changes will make these successful programs virtually unworkable. For this reason, the Administration

would favor a straight reauthorization over the enactment of these provisions. I will now review some of our specific concerns.

The discussion draft would require FDA, within 180 days, to issue a final rule to establish new criteria to reduce the period of market exclusivity to as low as 3 months, from the 6 months in the current statute. These criteria would include the amount of annual gross sales for all products with the same active moiety as the product, relative to research and development expenses for a requested study. Such a reduction in market exclusivity may be inappropriate because the value of improvements to children's health that may result from better use of drugs is very high. In addition, such a reduction could threaten the willingness of companies to conduct these costly but important trials, thus undermining the success of this program. As mentioned above, the current incentive of the 6 month period of exclusivity has worked well and should be maintained. Through this legislation, FDA has been able to effect important labeling changes on 128 different products. Any weakening of this incentive can only have the effect of reducing its effectiveness. Accordingly, proposals to shorten this incentive or to only provide exclusivity to drugs with one or more year left of patents and exclusivity life are of significant concern.

FDA supports greater internal cooperation; however, the draft bills' creation of an internal review committee for both BPCA and PRIA functions are of concern for a number of reasons. First, a legislative requirement for what are primarily staff functions is in direct conflict with the expertise, flexibility and efficiency needed to ensure rapid

review of pediatric product development. Second, the proposal assigns the dual function of approving written requests and granting exclusivity, which may result in conflicts between the subjective intent of the written request and the objective evaluation as to whether the studies fairly respond to the actual terms of written requests. Third, we believe that tracking pediatric studies are responsibilities more appropriately assigned to agency staff, since they are routine functions that do not require a decision-making body. Overall, these provisions could have the unintended consequence of creating a bottleneck through which all requests must flow and slowing the desired rapid and efficient review of pediatric product development. .

The PRIA discussion draft would require FDA to give priority review status for all supplements to new drug and biologics applications submitted as a result of PRIA. This would remove the flexibility FDA currently has in determining the appropriateness of the priority designation in relation to other priorities. By automatically assigning a preferential priority review to these submissions, that may not be priorities from a public health perspective, many other reviews currently deemed priority on the basis of medical judgment could no longer feasibly be completed within the priority review timeframes.

Finally, BPCA and PREA work in tandem to encourage and require pediatric studies that are vital to the health and welfare of pediatric patients. PREA helps to fill the need for those studies not addressed by BPCA, and we believe that it is important to keep these programs working side by side. Accordingly, we are concerned by the proposal to sunset BPCA, while there is no sunset provision in PRIA. It is important to have a wide

reaching voluntary program balanced with the more limited mandatory studies requirement.

It is critical that programmatic functions not be overburdened with additional requirements that could delay the decisions related to these programs or overburden the drug review system as a whole. FDA wants to build on the success of these programs to help ensure that the best pediatric information is available including critical labeling information that will be of value in treating children.

Pediatric Medical Devices

FDA is committed to supporting the development and availability of safe and effective pediatric medical devices. Designing pediatric medical devices can be challenging. Children are often smaller and more active than adults; body structures and functions change through childhood, and children may be long-term device users—bringing new concerns about device longevity and long-term exposure to implanted materials.

FDA's current initiatives include:

- Recruiting pediatric experts for FDA advisory panels whenever there is a reasonable likelihood that the device under discussion will be used for children;
- Protecting children who participate in clinical trials;
- Collaborating with the Institute of Medicine on the effectiveness of post-market surveillance of pediatric medical devices; and
- Collecting data on the unmet needs for pediatric medical devices and the barriers to the development of new pediatric devices.

However, the discussion draft raises several concerns. The draft would require FDA to track separately the adverse events associated with for-profit sales versus not-for-profit sales of pediatric devices. The public health benefit of such a requirement is unclear, a significant concern for an immensely complicated undertaking that would also represent a major retreat from FDA's recent effort to develop a modern, consolidated system for adverse event tracking.

The draft also would require an annual review of for-profit pediatric devices by the Pediatric Advisory Committee. This duplicative review imposes significant burden without a clear public health benefit.

The draft would also require FDA to cap the quantity of pediatric devices sold for profit and limits the profit making to only those devices indicated solely for pediatric populations, yet many of these devices are used in both adults and children. This approach may thus reduce the availability of safe and effective medical devices for pediatric populations and not provide the intended incentive for further pediatric device development.

Drug Safety

New drugs, biologics, devices, and diagnostics present the greatest opportunities currently available to improve health care and the way medicine is practiced. The number of lives saved that are prolonged by new therapies outweighs the risks that the treatments themselves pose. It is important to remember that no drug is absolutely

without risk and to recognize that sometimes information about the safety of a drug emerges after the drug is on the market. FDA approves a drug only after a sponsor demonstrates that the drug's benefits outweigh its risks for a specific population and a specific indication, and shows that the drug meets the statutory standards for safety and effectiveness. Because of practical limitations on how many patients can be studied for any given drug, the full array of potential risks does not necessarily always emerge during the mandatory clinical trials conducted before approval. Indeed, serious adverse effects may occasionally emerge after approval through post-marketing clinical trials or through spontaneous reporting of adverse events or both.

A robust post-marketing surveillance capacity could dramatically improve our ability to identify such safety issues, and address them before they become serious public health problems. Such a system must rely on both public and private resources and expertise, brought together in public-private partnerships. Such a partnership must have flexibility to assemble analytic and clinical experts and data resources from all sources. Such flexibility will also be crucial to ensure that the system can respond quickly to initiate new targeted safety surveillance in the face of a public health emergency.

However, attempts to address risks must balance access and innovation with regulatory steps to improve the approach to safety issues. Such steps should not impede access to new medical products that can be used safely and effectively by patients suffering from unmet medical needs today. While we want to add requirements when the science of drug safety validates their need, we want to avoid changes that will limit access to new medicines and slow down innovations while doing little to address drug safety.

Therefore, we have a number of key concerns with the bill as presently drafted. In particular, many of the provisions seem fixed on process and structural changes, and not on making fundamental improvements in the science of drug safety. Some changes prescribe specific Agency action when the science of drug safety may not require such intervention, such as the requirement to present all new molecular entities to advisory committees for discussion. Such changes could limit access to needed medicines and slow down new innovations while doing little to address the core issues of drug safety.

We are concerned by the breadth of the proposed requirements for risk evaluation and mitigation strategies outlined in the bill. We believe it is unnecessarily burdensome to require REMS, routine active surveillance and periodic reassessments for all drugs, as the legislation now does. The REMS approach would duplicate and overlap elements of the extensive adverse event reporting system already required by FDA (which includes incident-specific, quarterly, and annual reporting). It would also duplicate existing FDC Act labeling requirements, which provide for MedGuides, package inserts, and other materials which convey information to physicians and pharmacists (as well as patients) to address and minimize risk. Moreover, FDA and industry already engage in efforts with respect to implementation of risk minimization action plans ("RiskMAPs") for those products that warrant such additional risk minimization protocols. In addition, FDA already has authority to require post-approval studies in select circumstances. Codifying new authority is unnecessary.

Finally, the Drug Safety Oversight Board (DSOB) would be used to review disputes between the sponsor and FDA concerning REMS. Not only does the DSOB not have the necessary expertise to handle dispute resolutions, the bill proposes the disputes be raised directly to the DSOB. Since the DSOB would be the primary source of dispute resolution, this requirement would so overburden the DSOB that they will be unable to conduct their other important functions

Improved drug safety is not simply a matter of extending new legal authorities to FDA or requiring the Agency to engage in certain detailed activity. Indeed, extending these interventions or expanding the use of REMS is unlikely to result in improvements in drug safety as desired by the bill's sponsors.

The better overall strategy is to ensure that FDA has appropriate resources and the capacity to develop better scientific tools and approaches to drug review including: (1) improving information available to the Agency; (2) improving the Agency's ability to evaluate this information; and (3) improving how that evaluation is communicated to the public. Accordingly, the Administration's proposed PDUFA IV recommendations support such improvements with respect to:

- the information that the Agency receives, and with which it makes drug-safety related decisions, including the spontaneous reports we get from sponsors and providers as well as our ability to tap into new epidemiological data sets to probe more routine questions;
- our analytical tools and approaches for evaluating the information and turning raw data about drug-safety related questions into practical information that can be

communicated to providers and patients to help them better inform their decision-making; and

- the way in which we can effectively communicate these findings, as well as communicate the Agency's response once we draw a conclusion about the data we have, or are made aware of an emerging drug safety issue.

We also support the addition of provisions for an active drug safety surveillance system that would be established through a public-private partnership and we want to work with you on this provision to ensure the most effective implementation.

FDA actively engages with industry with respect to efforts to implement risk minimization action plans for those products that warrant such additional risk minimization steps. PDUFA IV would provide funds for developing a plan to evaluate current risk management plans and tools. We would obtain input from academia, industry, other government agencies, and other stakeholders regarding the prioritization of the plans and tools to be evaluated. The evaluation would include assessments of the effectiveness of identified RiskMAPS and current risk management and risk communication tools. Based on those evaluations, FDA would conduct an annual systematic review and public discussion of the effectiveness of one or two risk management programs and one major risk management tool. By making such information publicly available we would promote effective and consistent risk management and communication.

Our PDUFA IV proposal includes an increase in funding to improve the information technology (IT) infrastructure for human drug review, to move FDA toward an all-

electronic drug review system. We would use the increased PDUFA IV funds to improve our post-market safety-related IT systems to ensure the best collection, evaluation, and management of the vast quantity of safety data received by FDA. We would use these funds to improve our IT infrastructure to support access to and analyses of externally linked databases, and to enhance FDA's Adverse Event Reporting System and surveillance tools.

Preemption

Finally, we are concerned about new language on preemption in the discussion drafts, which states that nothing in the Act may be construed as having any legal effect on actions for damages under state law (including statutes, regulations, and common law). This language appears in each of the draft bills and relates to both drugs and devices.

With respect to drugs, FDA is the expert federal public health agency charged with ensuring that drugs are safe and effective and that the labeling adequately informs users of the drugs' risks and benefits. FDA reviews the pertinent scientific evidence and, through the drug approval process, provides formal, authoritative conclusions on the conditions under which drugs can be used safely and effectively. This provision in the draft bill could be interpreted to permit state law to undermine FDA's conclusions about drug labeling or about risk evaluation and mitigation strategies. We believe that State law actions that can conflict with the Agency's conclusions and frustrate the Agency's implementation of its public health mandate should not be endorsed in federal laws.

Conclusion

PDUFA III and MDUFMA expire on September 30, 2007, and I want to re-emphasize the importance of achieving a timely reauthorization of these laws. FDA is ready to work with you to accomplish this goal. If we are to sustain our record of accomplishment under PDUFA and MDUFMA, it is critical that these reauthorizations occur seamlessly without any gap between the expiration of the old laws and the enactment of the new ones.

In addition, FDA welcomes the opportunity to work with Congress to ensure that the benefits of the incentive program can continue, in conjunction with FDA's authority to require mandatory studies, as Congress considers the reauthorization of the BPCA and PREA programs.

FDA's mission is to promote and protect the public health. A major component of that mission is to ensure that the American public has access to safe and effective medical products. These statutes are essential to the fulfillment of our mission. We look forward to working with you.